Principles Guiding CAM Natural Product Research and Development

National Center for Complementary and Alternative Medicine (NCCAM)

Introduction

As NCCAM embarks on its second decade and the development of its third strategic plan, it remains committed to the rigorous investigation of herbal medicines, botanicals, dietary supplements, probiotics, and other natural products (NPs) that are used as complementary or alternative medicine (CAM) or that have origins in various alternative traditional medical systems. (For the purpose of this paper these are referred to collectively as CAM NPs). To that end and shaped by important lessons learned during its first decade, NCCAM staff has drafted a set of overarching principles intended to guide current thinking and future investment in this major and important component of NCCAM's overall research and development portfolio. These principles were the subject of a one-day stakeholder "Think Tank" held on the NIH campus on March 26, 2010. This document incorporates input received during discussions at that meeting. NCCAM invites public comment on the principles and other points discussed below.

Background and Lessons Learned

1. Need for Mechanistic Research

   To date, most large randomized efficacy trials of CAM NPs have failed to show hypothesized clinical benefits. Although in most cases there was a sound rationale for clinical trial design based on previous study results and other clinical experience, there have been frequent criticisms of these studies. These typically center on key aspects of study design (e.g., choice of product, dose, schedule of administration, outcome measures), and resultant uncertainty about the validity of "negative" findings. Many of these criticisms and doubts cannot be well addressed because most of these studies did not incorporate concomitant laboratory assessment of measures of biological effect or basic pharmacokinetics. On the basis of these experiences, it has become evident that the optimal approach to design of clinical *efficacy* studies of CAM NPs incorporates a *mechanistic* hypothesis and a measurement that provides a signature of the hypothesized biological effect. For example, pertinent markers of altered immune function would be incorporated into clinical trials studying Echinacea for viral infections if the hypothesis is that the herbal therapy works through modulation of immune function.

2. Need for Attention to Product Integrity

   The need for particular attention to the quality and integrity of NPs being studied in NCCAM-supported research has been and remains a major theme for the Center, and during its first decade NCCAM has led NIH in establishing rigorous standards in this regard. Two important points emerge

from an assessment of this extensive base of experience. First, modifications of NCCAM's Product Integrity Policy are underway that will more clearly link the level of informational detail required for a product with the complexity of the product and the types of research being carried out (e.g., more information is generally needed for large-scale clinical trials and less is needed for *in vitro* laboratory studies). Second, there remain major unaddressed needs for improved methodology for the characterization and analysis of NPs.

3. Need for Programmatic Focus

Historically, NCCAM has supported the vast majority of basic and translational research and development activities relevant to CAM NPs through general solicitations for investigator-initiated proposals. This broad-based approach has yielded a large body of basic mechanistic information and promising leads for future research. However, it cannot be relied on to ensure that critical gaps in knowledge and the development of essential translational tools (e.g., key pharmacological studies or development of relevant signatures of biological activity for use in subsequent clinical research) are filled, or that development of the most promising scientific opportunities or public health needs are pursued with goal-oriented clarity, timeliness, and efficiency. Accomplishing these activities will require the establishment of priorities for development, and the allocation of a portion of the Center's NP research and development resources to directed translational research and clinical development to address those priorities.

4. The Continuum of Exploratory Research-Targeted Development

For the purposes of this paper, we consider the organization of NCCAM's efforts in CAM NP research and development as a continuum. At one end are exploratory research activities with high potential to yield new, fundamental, mechanistic or physiological insight into the potential role or value of NP interventions in treating conditions or improving health. This work would include, for example, the investigation of previously unstudied NPs as well as new studies to obtain additional information about known products with a strong scientific rationale for interest. It also allows for serendipitous discoveries about the potential biological effects or applications of NPs. The expectation is that the range of products that are appropriate for exploratory research will be extensive, and that this work is appropriately supported through investigator-initiated research project grants.

At the other end of the continuum are CAM NPs that warrant and require targeted investment of resources toward definitive, goal-directed clinical development. In addition to clinical trials, work at this end of the continuum also includes key translational research needed to design maximally informative clinical studies. Given available resources, the expectation is that the number of CAM NPs entering large, advanced clinical trials will be small, and that these NPs will have been designated a high priority by NCCAM because of particularly promising preliminary results in smaller studies, or because of a compelling public health need (e.g., safety information).

PRINCIPLES GUIDING CAM NATURAL PRODUCT RESEARCH AND DEVELOPMENT

Exploratory Research

1. **Insight into the biological effects and potential mechanisms of action of CAM NPs is needed in order to pursue clinical research on and development of their potential.**

   As noted earlier and in the section on Targeted Development, insight into potential biological mechanisms of action and effects of NPs often has been lacking. An evidence-based hypothetical mechanism of action is central to the development of a maximally informative program of clinical research and development (see discussion below.)

2. **A variety of powerful technologies and tools (e.g., various "omics" methodologies) should be actively pursued to fill important gaps in knowledge of biological effects and mechanisms of action of CAM NPs.**

   These tools also offer promise for application to the complicated and challenging matter of exploration, including proof of concept studies of multi-component (e.g., additive, synergistic, or complementary) mechanisms that are at the core of most herbal traditions. Greater clarity about the activity of individual components may lead to a better understanding of possible synergistic effects.

3. **It is important to elucidate relationships between CAM NPs and host biology.**

   Many of the components in botanical products are complex molecules with low bioavailablity. Some of these molecules are metabolized by gut microflora, host digestive enzymes, or host metabolism, generating other compounds that may be more readily absorbed or bioactive. Little is known, however, about their possible bioactivity, or the organisms or processes that produce them. Furthermore, different outcomes across populations might be related to differences in host biology. Important examples of such phenomena include microbial induction of an active metabolite, equol, from soy daidzein, or the interactions of probiotics with endogenous microorganisms in the gut.

4. **Major needs remain for the development of better tools and methods for plant characterization and NP analysis.**

   Most of the techniques for the standardization and characterization of plants focus on the analysis of a limited number of abundant or easily detected and measured "marker" compounds. Better tools are needed to qualitatively, quantitatively, and universally capture the chemical diversity of complex (e.g., plant) NPs. Improved techniques also are needed for the isolation and characterization of polysaccharides, oligomeric polyphenols, and other botanical polymers that have been shown to contribute to biological activity.

5. **It is critical to look to various herbal traditions and other historical sources for promising leads regarding the potential of CAM NPs.**

   Alternative traditional medical systems from around the globe offer the potential for insight into the promise of herbal medicines deserving further study. For example, research built on the Ayurvedic traditions of India has pointed toward promising leads such as turmeric. Furthermore, in some cases access to these traditions is being lost rapidly either due to assimilation of the native cultures or extinction of the plants themselves. Information and knowledge from traditional medical systems and other historical sources should remain an important resource in considering the potential of CAM NPs and their priorities for research and development**.**

Targeted Development

1. **Criteria and processes should be established for identifying CAM NPs that merit NCCAM-supported, directed, targeted clinical development. Furthermore, the process of development should be guided by milestones intended to guide decisions about whether investment in further clinical research is justified.**

   NCCAM investment in large clinical trials of CAM NPs should be highly selective and should only be made when there is ample scientific and/or public health justification. Major factors to be considered in prioritization should include:

   - ∞ Potential for impact on an important medical or public health need (e.g., a new contribution to symptom management or promotion of health and wellness, or to a pressing concern regarding safety and public health)
   - ∞ Strength of existing preliminary data
   - ∞ Adequate research and quality control methodology (e.g., translational tools to measure biological effects, validated assays or processes for assuring product integrity)
   - ∞ Frequency and nature of use by the public.

   These factors, which must be weighed on a case-by-case basis, should serve as primary drivers in establishing priorities. In addition, a well-defined and transparent process for priority setting and oversight of milestone-driven processes should be established.

2. **Clinical trials of CAM NPs should be designed to be maximally informative, whether or not the hypothesized clinical outcomes are observed. In general, studies should be based on a scientifically plausible mechanistic hypothesis supported by basic/exploratory research; a sound body of pharmacokinetic/absorption, distribution, metabolism, and excretion (ADME) information; and the translational tools (e.g., concomitant laboratory measures of biological effect) needed to maximize knowledge gained.**

Pharmacokinetics/ADME: Understanding pharmacokinetics impacts many aspects of development as CAM NPs progress toward and into definitive clinical trials. Among these are knowledge about bioactive metabolites, bioavailability, and dosing protocols. Frequently, there is limited information on which component(s) of a complex product are essential for activities. This is further complicated by the possibility that active compounds are produced during metabolism. As a result, it can be challenging to know how to assess bioavailability when there are so many interrelated factors at work. Furthermore, this information directly affects decisions about the dosing schedule for the product of interest. Careful studies must be conducted to generate this critical information.

Translational tools to detect and measure signatures of biological effect and efficacy: Maximally informative, definitive clinical trials of CAM NPs require concomitant measures (i.e., signatures of biological effect) to determine whether the product actually exerts a relevant biological effect. Such measures are particularly important given the modest effect size of many NPs. In conjunction with pharmacokinetic data, these studies also might identify responsive patient populations.

Sensitive measures and creative trial designs: Clinical and laboratory measures of effect must be sensitive enough to detect the modest clinical effects expected for most CAM NPs, or to determine with a high degree of certainty that a negative result is truly negative. The high likelihood of modest effects on largely subjective clinical outcomes also calls for the exploration of novel clinical trial approaches, for example, adaptive crossover, or N-of-1 patient-centered designs.

3. There is need to continue efforts to explore the safety profile of specific CAM NPs.

It is often claimed or postulated that CAM NPs have fewer side effects or are "safer" than conventional pharmaceutical alternatives. However, there are well-documented examples of adverse herb-drug interactions (e.g., grapefruit juice or St. John's Wort and CYP enzymes), herb-herb interactions, contaminants, or product adulteration. Furthermore, there is limited information about the safety profile of most CAM NPs, including data about inherent toxicity, or interactions with drugs or other NPs. Given the widespread use of NPs by the public for self care and promotion of wellness – often independent of professional advice – investigation of the short- and long-term safety of these products, including their possible interactions with pharmaceuticals and with other NPs, remains a compelling public health need.